CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA

Momfluorothrin

Chemical Code # 6208**, Document Processing Number (DPN)** 53304
SB 950 # NA
6/3/15

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect indicated
Chronic toxicity, dog:	No data gap, no adverse effect indicated
Oncogenicity, rat:	No data gap, possible adverse effect indicated
Oncogenicity, mouse:	No data gap, no adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect indicated
Developmental toxicity, rat:	No data gap, no adverse effect indicated
Developmental toxicity, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, possible adverse effect indicated
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	No data gap, no adverse effect indicated

Toxicology one-liners are attached.

All record numbers for the above study types through 279007 (Document No. 53304-0033) were examined. This includes all relevant studies indexed by DPR as of 6/3/15.

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T150603
Revised by T. Moore, 6/3/15

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

Metabolism, Rat

55504-0030; 279004; **"**The Disposition and Metabolism of S-1563RTZ and S-1563RTE in Rats (a single administration); (K. Mikata; Environmental Health Sciences Laboratory, Sumitomo Chemical Company, Ltd., Konohanu-ku, Osaka, Japan; Study No. 4132; 10/14/11); Wistar rats of both sexes were treated with 1 or 250 mg/kg of [Cyclopropyl-1-^{14}C]S-1563RTZ (lot no. CFQ40197, specific activity: 2.26 GBq/mmol, radiochemical purity: 99.7%) or 1 or 25 mg/kg of [Cyclopropyl- 1-^{14}C]S-1563RTE, lot no. CFQ40198, specific activity: 2.26 GBq/mmol, radiochemical purity: 99.5%) Dosing preparations were supplemented with non-labeled S-1563RTZ (lot no. SK080616, purity: 99.8%) or non-labeled S-1563RTE (lot no. SK080605, purity: 99.8%). In the Excretion Study, four animals/sex/group were dosed orally by gavage with one or the other test material at the two treatment levels and urine and fecal samples were collected up to 7 days post-dose. Air samples were collected through 24 hours in the 1 mg/kg treatment regimens. In the Biliary Excretion Study, four animals/sex, whose bile ducts had been cannulated, were dosed with 1 mg/kg of one or the other test material. Bile, urine and fecal samples were collected through 72 hours post-dose. In the Pharmacokinetics Study, 3 animals/sex/group were dosed with one or the other of the test materials at the two treatment levels and blood samples were drawn at specified time intervals up to 5 days post-dose. In the Tissue Distribution Study, 9 animals/sex/group were dosed with one or the other of the two test materials at both treatment levels and 3 animals/sex/group/time point were euthanized at specified time intervals post-dose and the concentration of radiolabel in particular tissues was determined. In the Excretion Study, slightly more of the radiolabel was excreted in the urine of the females than the males at a treatment level of 1 mg/kg (66 vs. 47% for RTZ and 81 vs. 67% for RTE). This relationship was also true for the higher treatment levels. Air sampling recovered 0.1% of the administered dose. Seventy eight to 95% of the administered dose was recovered in the 1st 24 hours post-dose, regardless of the test material, sex of the animal or treatment level. In

the Biliary Excretion Study, 47 to 60% of the dose was recovered in the bile. Overall, absorption of the test materials ranged from 82 to 94%. In the pharmacokinetic study, the time to peak concentration in the plasma (Tmax) was 4 or 8 hours at the lower treatment levels, increasing to 12 hours for the 250 mg/kg treatment. The highest achieved concentration in the plasma (Cmax) was 50 to 100% higher for the females at the same treatment level. The $T_{1/2}$ for the S-1563RTZ ranged from 10.8 to 18.5 hours. The $T_{1/2}$ for the S-1563RTE ranged from 7.6 to 29.3 hours. The liver, kidneys and gastrointestinal tract were the primary sites of radiolabel recovery over the first 48 hours post-dose. By 7 days post-dose, tissue levels were negligible. Radioassay of the stomach, small intestine, cecum and large intestine contents demonstrated a time-course of passage for the radiolabeled compound through the gastrointestinal tract. The radiolabel was not appreciably sequestered in the fat nor did a significant fraction of the administered dose pass across the blood:brain barrier. Based upon the isolated metabolites, the major pathways of metabolism for both isomers were 1) cleavage of the ester linkage, 2) demethylation of the methoxymethyl group, 3) oxidation of the methyl group on the cylclopropyl and/or propenyl groups, 4) conjugation with glucuronide and 5) isomerization of the glucuronide conjugates. For the S-1563RTZ isomer, conjugation of the propenyl group with sulfonic acid and oxidation or reduction of the double bond in the propenyl group were also delineated. **Study acceptable.** (Moore, 4/1/15)

53304-0029; 279003; "Metabolism of S-1563RTZ in Rats-Disposition, Metabolism and Excretion of S-1563RTZ in Rats after Repeated Oral Administration"; (K. Hayashi; Kumamoto Laboratory, Mitsubishi Chemical Medience Corporation, Uto-shi, Kumamoto 869-0425, Japan; Study No.P090160; 12/25/09); Twenty male Wistar rats were dosed orally by gavage with 1.0 mg/kg/day of [Cyclopropyl-1-^{14}C]S-1563RTZ (lot no. CFQ40197, specific activity: 2.26 GBq/mmol, radiochemical purity: 99.7%) for 21 days. Non-labeled S-1563RTZ (lot no. SK080616, purity: 99.8%) was used to supplement the dosing preparations. Three animals/time point were euthanized at 6 hours post-dose on days 10, 16 and 21 and at 7 and 14 days post-final dose. The distribution of radioactivity in the tissues/organs was assessed at these time points. Urine and feces were collected daily throughout the dosing period and during the 14-day post-final dose observation period. Metabolites were isolated and identified in the urine, feces, plasma, red blood cells, liver, kidneys and hair. Ninety eight percent of the cumulative administered dose was recovered in the urine or feces by 14 days post-final dose. Fifty six percent of the total dose was recovered in the feces and 42% in the urine. The liver, kidneys and gastrointestinal tract were the primary sites of radiolabel recovery over the 21-day treatment period. Thereafter, the levels of radioactivity in these tissues/organs declined appreciably. In contrast, the hair, plasma, and red blood cells did not have high levels of radioactivity during the treatment period, but the radioactivity levels persisted through the 14-day post-final dose period. Based upon the isolated metabolites, the major pathway of metabolism was 1) cleavage of the ester linkage, 2) demethylation of the methoxymethyl group, 3) oxidation of the methyl group on the cylclopropyl and/or propenyl groups , and 4) conjugation with glucuronide,. Metabolites, Z-CMCA (cleavage of the ester linkage), 2CHM-CMCAZ (oxidation of the cyclopropyl group) and ωHM-CMCAZ (oxidation of the propenyl group) were recovered in the urine and feces and all of the other sites which were assayed. The conjugated glucuronide products were only recovered in the urine and kidneys. **Study supplemental.** (Moore, 4/6/15)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

0014; 278967; "Acute Oral Toxicity Study of S-1563 in Rats" (Deguchi, Y., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. 4166 (RWT-0010), 07/30/2010). 870.1100. S-1563 (Lot No. KY090520G, purity = 95.2%) was suspended in corn oil and administered in a single dose by gavage to 5 Crl:CD(SD) rats per sex per dose at dose levels of 0, 50, 300, and 2000 mg/kg. Mortalities occurred as follows- males: 0/5, 0/5, 0/5, 2/5, respectively; females: 0/5, 0/5, 0/5, 5/5, respectively. Clinical signs observed in males at 300 and 2000 mg/kg after dosing included tremors, urinary incontinence, and perianal staining; clonic convulsions, perioral and perinasal staining, and stains of the abdomen were also observed at 2000 mg/kg. Clinical signs observed in females at 2000 mg/kg included tremors, salivation, urinary incontinence, clonic convulsions, and tip toe gait. Necropsy revealed no treatment-related abnormalities. 300 mg/kg< LD_{50} (M/F)< 2000 mg/kg. Toxicity Category II. NOEL (M) = 50 mg/kg, NOEL (F) = 300 mg/kg (based on absence of clinical signs). **Acceptable**. (Corlett, 09/02/2014)

Acute dermal toxicity

0014; 278968; "Acute Dermal Toxicity Study of S-1563 in Rats" (Deguchi, Y., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. 4167 (RWT-0017), 06/24/2010). 870.1200. S-1563 (Lot No. KY090520G, purity = 95.2%) was applied to sheared dorsal skin of 5 Crl:CD(SD) rats per sex per dose at dose levels of 0 and 2000 mg/kg by placing the test material on a gauze sheet moistened with injection water and spreading the test article evenly on the gauze using a spatula with a small quantity of injection water. The treated area was then occluded with an impermeable gauze sheet for 24 hours. No mortalities occurred. No clinical signs were observed. Necropsy revealed no treatment-related abnormalities. Reported LD_{50} (M/F) > 2000 mg/kg. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of documentation demonstrating that the procedure used in moistening the test article sufficiently moistened the test article to ensure good contact with the skin. (Corlett, 09/03/2014)

Acute inhalation toxicity, rat

0014; 278969; "Acute Inhalation Toxicity Study of S-1563 in Rats" (Deguchi, Y., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. 4168 (RWT-0021), 07/01/2011). 870.1300. S-1563 (Lot No. 9CM0109G, purity = 95.7%) was aerosolized via a dust feeder and administered in a nose-only manner to 5 Crj:CD(SD) rats per sex per dose at dose levels (mean gravimetric concentrations) of 581, 1100, and 2030 mg/m^3 (with MMADs (GSDs) of 5.00 (2.76), 3.73 (3.14), and 4.86 (2.56) µm, respectively) for 4 hours. Mortalities occurred as follows- males: no mortalities; females: 0/5, 0/5, 1/5 (during the fourth hour of exposure), respectively. Clinical signs observed in the males included wet fur (in all animals at all dose levels), staining around the snout (at 1000 mg/m^3 and 2000 mg/m^3) and eyes (at 1000 mg/m$^{3)}$, ataxic gait (in 1 animal at 500 mg/m^3 and in 1 animal at 2000 mg/m^3 2 hours after exposure), hypersensitivity (in 3 and 4 animals at 2000 mg/m^3 1 and 2 hours after exposure, respectively), and muscular rigidity (in 1 animal at 2000 mg/m^3 1 hour after exposure) with all of these signs clearing in all animals 2 days after exposure. Clinical signs observed in the females included wet fur (in all animals at all dose levels), staining around the snout (at 1000 mg/m^3 and 2000 mg/m^3) and eyes (at 1000 mg/m^3), ataxic gait (in 1 animal at 1000 mg/m^3 2 hours after exposure and in 3 and 4 animals at 2000 mg/m^3 2 hours after exposure and 1 day after

exposure, respectively), tip toe gait (in 4 animals at 2000 mg/m^3 2 and 3 days after exposure), tremors (in 1 animal at 500 mg/m^3 1 hour after exposure and in 1 animal at 2000 mg/m^3 during the 3rd hour of exposure), tremor of the tail (in 2 animals at 2000 mg/m^3 during the 2nd hour of exposure), hypersensitivity (in 1 animal at 2000 mg/m^3 1 hour after exposure), and muscular rigidity (in 2 animals at 500 mg/m^3 2 hours after exposure and in 1 animal 1 day after exposure) with all of these signs clearing in all surviving animals 4 days after exposure. Necropsy revealed no treatment-related abnormalities. LC_{50} (M/F) > 2030 mg/m^3. Toxicity Category IV. **Acceptable**. (Corlett, 09/05/2014)

Primary eye irritation, rabbit

0014; 278970; "Eye Irritation Test of S-1563 in Rabbits" (Ota, M., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. 4140 (RWT-0014), 01/28/2011). 870.2400. 0.1 ml (0.061 g) of S-1563 (Lot No. KY090520G, purity = 95.2%) was placed into the conjunctival sac of 1 eye of each of 6 New Zealand White rabbits (3 of the treated eyes were washed and 3 were not washed). No corneal opacity was observed in any unwashed treated eye. Grade 1 iritis was observed in 2 unwashed treated eyes 1 hour after treatment with all signs of iritis clearing in all treated eyes 24 hours after treatment. Grade 1 conjunctival irritation was observed in all 3 unwashed treated eyes 24 hours after treatment with all signs of conjunctival irritation clearing in all treated eyes 48 hours after treatment. Toxicity Category III. **Acceptable**. (Corlett, 09/10/2014)

Primary dermal irritation

0014; 278971; "Skin Irritation Test of S-1563 in Rabbits" (Ota, M., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. 4141 (RWT-0015), 01/28/2011). 870.2500. 0.5 g of S-1563 (Lot No. KY090520G, purity = 95.2%) was spread evenly on a lint patch which was moistened with 0.5 ml of corn oil and the patch was applied to the clipped dorsal skin of each of 3 New Zealand White rabbits for 4 hours using a semi-occlusive covering. No treatment-related skin irritation was observed during a 72-hour observation period. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of documentation demonstrating that the procedure used in moistening the test article sufficiently moistened the test article to ensure good contact with the skin and a justification why corn oil and not an aqueous vehicle was used to moisten the test article . (Corlett, 09/11/2014)

Dermal sensitization

0014; 278972; "Skin Sensitization Test of S-1563 in Guinea Pigs (Maximization Test)" (Ota, M., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. 4196 (RWT-0012), 10/25/2010). 870.2600. The Magnusson and Kligman maximization assay was used to assess the potential S-1563 (Lot No. KY090520G, purity = 95.2%) to elicit delayed contact hypersensitivity in the guinea pig. 20 Hartley (SPF) guinea pigs were treated with the test material at induction (intradermal injections followed by a topical application 7 days later) and at challenge (a topical application 2 weeks after the topical induction). A concurrent negative control group consisting of a group of 10 animals was also included in the study. The control animals were treated identically to the test animals, except that during induction, the test material was replaced with the vehicle (acetone). The positive control was functional. The challenge sites were examined for erythema 24 and 48 hours after challenge patch removal; no positive reactions were observed in any treatment group animals. **The results of the study indicate that the test material is a not sensitizer when using this**

modified version of the Magnusson and Kligman maximization test. Acceptable. (Corlett, 09/22/2014)

SUBCHRONIC STUDIES (units of mg/kg/day unless specified)

Rat Subchronic Dietary Toxicity Study

0015; 278973; "S-1563 13-Week Repeated Dose Oral (Feeding) Toxicity Study in the Wistar Rat Followed by a 6-Week Recovery Period" (Sommer, E.W., Harlan Laboratories Ltd., Itingen, Switzerland, Harlan Laboratories Study C37995, RWT-0011, 10/18/2011). 870.3100. S-1563 (Batch Number 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 12 HanRcc:WIST (SPF) rats per sex per dose at dose levels of 0 (diet only), 300, 1000, 3000, or 6000 ppm (for males, 0, 23.03, 75.82, 223.36, and 484.98 mg/kg/day, respectively, and for females, 0, 24.75, 81.54, 236.06, and 500.92 mg/kg/day, respectively) for 13 weeks (6 additional rats per sex at the 0 and 6000 ppm dose levels were not sacrificed at week 13 and were used to assess recovery over a subsequent 6-week treatment-free period). All animals survived to the scheduled necropsy. No treatment-related clinical signs were observed during the daily clinical observations or during the weekly detailed physical observations. FOB and locomotor activity assessments revealed no treatment-related effects in main group animals or in the recovery group animals. A treatment-related decrease in mean body weight was observed in both sexes at 3000 and 6000 ppm with this effect persisting in the recovery group animals. A treatment-related decrease in mean corpuscular volume and mean corpuscular hemoglobin levels were observed in both sexes at 6000 ppm and a treatment-related increase in mean reticulocyte count was observed in males at 3000 and 6000 ppm and in females at 6000 ppm; none of these hematological effects persisted in the recovery group animals. Treatment-related increases in the mean cholesterol and mean phospholipids levels (in both sexes at 1000, 3000, and 6000 ppm) and in the mean gamma-glutamyl-transferase level (in both sexes at 3000 and 6000 ppm) were observed with this increase in cholesterol persisting in the recovery group animals but this was not the case for the other two parameters. A treatment-related increase in mean relative liver weight was observed in both sexes at 3000 and 6000 ppm and this effect persisted in the recovery group animals. Macroscopic examination of the internal organs revealed a treatment-related increase in enlarged livers in males at 3000 and 6000 ppm; the recovery group animals did not exhibit enlarged livers. Microscopic examination revealed treatment-related hepatocellular hypertrophy in males at 3000 and 6000 ppm and in females at 6000 ppm (not present in the recovery group animals), treatment-related brownish pigment in the liver in both sexes at 1000, 3000, and 6000 ppm (persisting in 3/6 males and 1/6 females in the recovery group), and treatment-related brownish pigment in the kidneys in both sexes at 3000 and 6000 ppm (persisting in 5/6 males and 5/6 females in the recovery group). **No adverse effects**. NOEL (M) = 23.03 mg/kg/day (300 ppm) and NOEL (F) = 24.75 mg/kg/day (300 ppm) based on an increase in mean cholesterol and phospholipids levels and brownish pigment in the liver. **Acceptable.** (Corlett and Leung, 11/13/2014)

Dog Subchronic Oral Toxicity Study

0016; 278974; "S-1563 13-Week Repeated Dose Oral (Capsule) Toxicity Study in the Beagle Dog Followed by a 6-Week Recovery Period" (Braun, L., Harlan Laboratories Ltd., Itingen, Switzerland, Harlan Laboratories Study C61698, RWT-0036, 12/09/2011). 870.3150. S-1563 (Batch Number 9CM0109G, purity = 95.7%) was administered orally by capsule once daily to 4 pure-bred Beagle dogs per sex per dose at dose levels of 0 (empty capsule(s)), 50, 200, or 600 mg/kg/day for 13 weeks with 2 additional dogs per sex at the 0 and 600 mg/kg/day dose levels

that were used to assess recovery over a subsequent 6-week treatment-free period. All animals survived to the scheduled necropsy. The daily clinical observations revealed an increase in incidence of loose, watery feces and vomiting of mucus or feed in both sexes at 600 mg/kg/day; this increase in incidence was not observed in the recovery group animals. No treatment-related clinical signs were observed during the weekly detailed physical observations. No treatment-related effects on body weight were observed. No treatment-related changes in hematology parameters were observed. A treatment-related increase in the mean cholesterol levels (in both sexes at 600 mg/kg/day) was observed along with a trend toward increased mean levels of trigylcerides (in both sexes at 600 mg/kg/day); these changes were not observed in the recovery group animals. A treatment-related (although not statistically significant) increase in mean relative liver weight was observed in both sexes at 600 mg/kg/day; this change was not observed in the recovery group animals. Necropsy revealed no treatment-related macroscopic findings. Microscopic examination revealed treatment-related centrilobular hepatocellular hypertrophy in both sexes at 600 mg/kg/day; this change was not observed in the recovery group animals. **No adverse effects**. NOEL (M/F) = 200 mg/kg/day based on an increase in mean cholesterol and triglycerides levels, an increase in mean relative liver weights, and centrilobular hepatocellular hypertrophy. **Acceptable.** (Corlett and Leung, 11/24/2014)

Rat 28-Day Repeated Dosing Dermal Toxicity Study

0017; 278975; "A 28-Day Repeated Dose Dermal Toxicity Study of S-1563 in Rats" (Ogata, H., Mitsubishi Chemical Medience Corporation, Kumamoto, Japan, Study No., P111028, RWT-0065, 08/30/2012). 870.3200. S-1563 (Lot number 9CM0109G, purity = 95.7%) was applied to a gauze sheet, the gauze sheet moistened sufficiently with water, and the gauze sheet/test article was applied to the clipped dorsal region of 10 Crl:CD(SD) rats per sex per dose at dose levels of 0 (vehicle control), 100, 300, and 1000 mg/kg once daily for 6 hours using an occlusive wrap for 28 days. No mortalities occurred. No treatment-related clinical signs were observed throughout the study during the daily observations or during the weekly detailed clinical observations. No treatment-related effects on mean body weight or mean food consumption were observed. Hematology, blood biochemistry, and urinalysis revealed no toxicologically significant changes. No treatment-related effects on organ weights were observed. Necropsy revealed no treatment-related gross observations. Microscopic examination revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M/F, systemic) = 1000 mg/kg/day based on no effects at the highest dose tested. **Acceptable**. (Corlett and Leung, 12/02/2014)

Four-Week Repeated Inhalation Toxicity Study

0033; 279007; "Four-Week Repeated Inhalation Toxicity Study of S-1563 in Rats" (Deguchi, Y., Sommer, E.W., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. 4218, RWT-0037, 10/25/2011). S-1563 (Batch Number 9CM0109G, purity = 95.7%) was aerosolized (dust aerosol) and administered in a nose-only manner to 10 Crl:CD (SD) rats per sex per dose at dose levels (mean gravimetric concentrations) of 0 (air control), 57.3, 159, and 313 mg/m^3 (mean MMADs (GSDs) of 4.49 (2.95), 5.00 (2.57), and 5.07 (2.49) µm, respectively) for 4 continuous hours per day for 28 (males) and 29 (females) consecutive days. No mortalities occurred. An increase in incidence of wet fur in both sexes at 159 and 313 mg/m^3 was observed throughout the 28-29 day exposure period. Ataxic gait (observed in 1 animal before dosing on day 2, clearing 1 hour after dosing on day 2), muscular rigidity (observed in 1 animal before dosing on day 3, clearing 1 hour after dosing on day 3), hypersensitivity (observed in 1 animal 1 hour after exposure on day 28 clearing by day 29), and tremor (observed in 1 animal 1 hour after dosing on day 1 clearing by day 2) were treatment

related clinical signs observed in males at 313 mg/m^3; treatment-related tip toe gait was observed in 1 female at 159 mg/m^3 and 1 female at 313 mg/m^3 on day 2 before dosing clearing in both 1 hour after dosing. No treatment-related effects on body weight and food consumption were observed. Hematological investigations revealed no treatment-related effects. Treatment-related increases in the mean cholesterol (in both sexes at 159 and 313 mg/m^3), in the mean phospholipids (in females at 159 and 313 mg/m^3) and in the mean aspartate aminotransferase (in males at 313 mg/m^3) levels and a treatment-related decrease in the mean glucose (in males at 313 mg/m^3) level were observed. Urinalysis revealed no treatment-related effects. A treatment-related increase in mean relative liver weight was observed in both sexes at 159 and 313 mg/m^3. Necropsy revealed no treatment-related macroscopic findings. Histopathological examination revealed no effects of toxicological significance. **Possible adverse effect**: **ataxic gait, tremor, and tip toe gait observed.** NOEL (M/F) = 57.3 mg/m^3 (mean gravimetric concentration) based on clinical signs and increased mean relative liver weight. **Supplemental study** (not a guideline study). (Corlett and Leung, 03/30/2015)

CHRONIC STUDIES

Chronic Toxicity, Rat

0018; 278976; "S-1563 52-Week Chronic Toxicity (Feeding) Study in the Wistar Rat" (Rached, E., Harlan Laboratories Ltd., Itingen, Switzerland, Harlan Laboratories Study C66200, RWT-0038, 12/16/2011). 870.4100. S-1563 (Batch Number 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 21 RccHan:WIST (SPF) rats per sex per dose at dose levels of 0 (diet only), 200, 500, 1500, or 3000 ppm (for males, 0, 10.5, 27.4, 82.6, and 168.7 mg/kg/day, respectively, and for females, 0, 12.4, 33.5, 103.1, and 199.1 mg/kg/day, respectively) for 52 to 53 weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed during the daily clinical observations or during the weekly detailed physical observations. FOB and locomotor activity assessments conducted during week 52 revealed no treatment-related effects. A treatment-related decrease in mean body weight was observed in males (not statistically significant) at 3000 ppm and in females at 500, 1500, and 3000. Food consumption was reduced (with and without attaining statistical significance) throughout the study in females at 3000 ppm. A treatment-related decrease in mean corpuscular volume was observed in both sexes at 1500 and 3000 ppm at week 52. Treatment-related increases in mean cholesterol and phospholipids levels (in both sexes at 1500 and 3000 ppm at weeks 13, 26, and 52), in the mean triglycerides level (at 3000 ppm in males at weeks 13 and 26 and in females at week 13), and in the mean gamma-glutamyl-transferase level (in both sexes at 1500 and 3000 ppm at weeks 13, 26, and 52). A treatment-related increase in mean relative liver weights was observed in males at 1500 and 3000 ppm and in females at 500, 1500, and 3000 ppm. Macroscopic examination of the internal organs revealed a treatment-related increase in enlarged livers in males at 1500 and 3000 ppm. Microscopic examination revealed treatment-related hepatocellular hypertrophy in males at 1500 and 3000 ppm and in females at 500, 1500, and 3000 ppm, treatment-related brownish pigment in the liver in both sexes at 1500 and 3000 ppm, treatment-related brown pigment in the tubular cells of the kidneys in both sexes at 1500 and 3000 ppm, and treatment-related bile duct proliferation in females at 3000 ppm. **No adverse effects**. NOEL (M) = 27.4 mg/kg/day (500 ppm) and NOEL (F) = 12.4 mg/kg/day (200 ppm) based on an increase in mean relative liver weights, brownish pigment in the liver, and hepatocellular hypertrophy. **Acceptable.** (Corlett and Leung, 12/10/2014)

Chronic Toxicity, Dog

0019; 278977; "S-1563: 52-Week Repeated Dose Oral (Capsule) Toxicity Study in the Beagle Dog" (Braun, L., Harlan Laboratories Ltd., Itingen, Switzerland, Harlan Laboratories Study C93211, RWT-0044, 06/08/2012). 870.4100. S-1563 (Batch Number 9CM0109G, purity = 95.7%) was administered orally by capsule once daily to 4 pure-bred Beagle dogs per sex per dose at dose levels of 0 (empty capsules), 25, 100, or 400 mg/kg/day for 52 weeks. All animals survived to the scheduled necropsy. The daily clinical observations revealed an increase in incidence of watery or mucous feces in both sexes at 100 and 400 mg/kg/day and vomiting of mucus or feed in females at 100 mg/kg/day and in both sexes at 400 mg/kg/day. No treatment-related clinical signs were observed during the weekly detailed physical observations. No treatment-related effects on body weight were observed. No treatment-related changes in hematology parameters were observed. A treatment-related increase in the mean trigylcerides level in males at 400 mg/kg/day at weeks 4, 8, and 13 and in females at 400 mg/kg/day at weeks 4 and 8. Urinalysis revealed no treatment-related changes. No treatment-related effects on the mean absolute or mean relative organ weights were observed. Necropsy revealed no treatment-related macroscopic findings. Microscopic examination revealed treatment-related minimal brownish pigment deposition in periportal hepatocytes in both sexes at 400 mg/kg/day and hepatocellular hypertrophy (periportal prominent) in 1 female and 2 males at 100 mg/kg/day and in all animals in both sexes at 400 mg/kg/day. **No adverse effects**. NOEL (M/F) = 25 mg/kg/day based on an increase in incidence of watery or mucous feces and vomiting of mucus or feed and hepatocellular hypertrophy (periportal prominent). **Acceptable.** (Corlett and Leung, 12/17/2014)

Oncogenicity, Rat

0020; 278978; "S-1563: 104-Week Oncogenicity (Feeding) Study in the Wistar Rat" *(Rached, E., Harlan Laboratories Ltd., Itingen, Switzerland, Harlan Laboratories Study* C66211, RWT-0070, 10/19/2012). 870.4200. S-1563 (Batch Number 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 51 RccHan:WIST (SPF) rats per sex per dose at dose levels of 0 (diet only), 200, 500, 1500, or 3000 ppm (for males, 0, 9.5, 23, 73, and 154 mg/kg/day, respectively, and for females, 0, 11.1, 28, 88, and 182 mg/kg/day, respectively) for 104 weeks. No treatment-related mortalities occurred; the survival percentage of all dose groups was greater than 25%. No treatment-related clinical signs were observed during the daily clinical observations. Detailed clinical observations revealed no treatment-related findings including no treatment-related increase in the incidence in the number or type of masses observed grossly. A treatment-related decrease in mean body weight was observed in males at 1500 and 3000 ppm and in females at 500, 1500, and 3000. No treatment-related effect on mean absolute food consumption was observed. No treatment-related effects on the hematology parameters (leukocytes) were observed after 52, 78, and 104 weeks. A treatment-related increase in mean relative liver weights was observed in both sexes at 1500 and 3000 ppm. Necropsy revealed treatment-related increases in the incidence of nodules and cysts in the liver of both sexes at 3000 ppm and in the incidence of nodules in the liver of males at 1500 ppm. Microscopic examination revealed treatment-related hepatocellular hypertrophy and brownish pigment in the liver in both sexes at 1500 and 3000 ppm, cystic degeneration in the liver of males at 1500 and 3000 ppm, biliary cysts in the liver of both sexes at 3000 ppm, and brownish pigment in the renal tubules in males at 3000 ppm and in females at 1500 and 3000 ppm. Increased incidences of eosinophilic cell foci (in both sexes at 3000 ppm) were observed. Also, the incidences of hepatocellular adenomas, of hepatocellular carcinomas, and of the total number of animals with

hepatocellular adenoma and/or carcinoma were increased in males at 1500 ppm and in both sexes at 3000 ppm. Possible adverse effect indicated: treatment-related hepatocellular adenomas and carcinomas. NOEL (M) = 23 mg/kg/day (500 ppm) and NOEL (F) = 11.1 mg/kg/day (200 ppm) based on a decrease in mean body weights, an increase in mean relative liver weights, an increase in incidence of brownish pigment in the liver, and an increase in incidence of hepatocellular hypertrophy. Acceptable. (Corlett and Leung, 01/05/2015)

Oncogenicity, Mouse

0021; 278979; "S-1563: 78-Week Oncogenicity (Feeding) Study in the CD-1 Mouse" (Rached, E., Harlan Laboratories Ltd., Itingen, Switzerland, Harlan Laboratories Study C76177, RWT-0052, 07/18/2012). 870.4200. S-1563 (Batch Number 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 52 CD-1 mice per sex per dose at dose levels of 0 (diet only), 600, 2500, or 5500 ppm (for males, 0, 72, 308, and 639 mg/kg/day, respectively, and for females, 0, 99, 427, and 853 mg/kg/day, respectively) for at least 78 weeks (main group) with 12 additional animals per sex per dose sacrificed after being treated for 52 weeks (satellite group). No treatment-related mortalities occurred; the survival percentage of all dose groups was greater than 25%. No treatment-related clinical signs were observed during the daily clinical observations. Detailed clinical observations revealed no treatment-related findings including no treatment-related increase in the incidence in the number or type of masses observed grossly. A treatment-related decrease in mean body weight was observed in the main group males at 2500 and 5500 ppm but not in females. A treatment-related decrease in mean absolute food consumption was observed in both main group sexes at 5500 ppm. No treatment-related effects on the hematology parameters (leukocytes) were observed after 52 and 78 weeks. A treatment-related increase in mean relative liver weights was observed in both satellite and main group animals of both sexes at 2500 and 5500 ppm. Necropsy revealed no treatment-related macroscopic findings in the main group or in the satellite group animals. Microscopic examination revealed treatment-related hepatocellular hypertrophy in the main group animals of both sexes at 2500 and 5500 ppm (this effect was also observed in satellite group females at 2500 and 5500 ppm) and brownish pigment in the liver in both sexes of the main group animals at 5500 ppm. Micropathological examination revealed no treatment-related neoplastic tumors in the satellite group animals or in the main group animals. No adverse effects indicated. NOEL (M) = 72 mg/kg/day (600 ppm) and NOEL (F) = 99 mg/kg/day (600 ppm) based on a decrease in mean body weights (in males), an increase in mean relative liver weights, an increase in incidence of brownish pigment in the liver, and an increase in incidence of hepatocellular hypertrophy. Acceptable. (Corlett and Leung, 01/14/2015)

GENOTOXICITY

Gene mutation

0025, 278994; "Reverse Mutation Test of S-1563 in Bacterial Systems" (Kitamoto, S., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, RWT-0004, Study No. 4142, 12/01/2009). 870.5100. Triplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* WP2 *uvrA* were pre-incubated with S-1563 (Lot No. 9CM0109G, purity = 95.7%), in the presence and absence of S9 rat liver fraction mix, at 0 (DMSO), 156, 313, 625, 1250, 2500, and 5000 ug/plate. This was followed by plating and further incubation for 48 hours at 37°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. Negative results indicate that under these

test conditions the test article is not mutagenic in these tested strains. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 02/06/2015)

0025, 278995; "Gene Mutation Assay in Chinese Hamster V79 Cells *In Vitro* (V79/HPRT) with S-1563" (Wollny, H.E., Harlan Cytotest Cell Research GmbH, Rossdorf, Germany, RWT-0026, Harlan CCR Study 1397600, 08/08/2011). 870.5300. Cultures of the Chinese hamster V79 cell line (HPRT locus) were treated with S-1563 (Lot No. 9CM0109G, purity = 95.7%) in 2 complete main experiments (each with and without exogenous Wistar rat liver S9 metabolic activation) using 2 parallel cultures each with each culture using 2 flasks (replicates). In the first experiment, the cells (both with and without metabolic activation) were treated for 4 hours at concentrations of 0 (untreated cells only), 0 (DMSO, the vehicle), 7.7 (non-activated only), 15.3, 30.5, 61.0, 76.8 (activated only), 91.5, 106.8 (activated only), and 122.0 ug/ml. In the second experiment, the cells were treated for 4 hours and 24 hours, activated and non-activated, respectively, at concentrations of 0 (untreated cells only), 0 (DMSO, the vehicle), 7.7, 15.3, 30.5, 61.0, 76.8 (activated only), 91.5, and 122.0 ug/ml (non-activated only). Positive controls of ethylmethane sulphonate (non-activated) and 7,12-dimethylbenz(a)anthracene (activated) were used in each experiment: the positive controls were functional. No evidence of mutagenic effects was observed in this mammalian forward mutation system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 02/12/2015)

Chromosome damage

0025, 278996; "*In vitro* Chromosomal Aberration Test on S-1563 in Chinese Hamster Lung Cells (CHL/IU)" (Kitamoto, S., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, RWT-0005, Study No. 4143, 12/25/2009). 870.5375. Duplicate cultures of Chinese hamster lung cells were treated with S-1563 (Lot No. 9CM0109G, purity = 95.7%) in 2 experiments. In Experiment 1, the cell cultures were treated with the test article at dose levels of 0 (DMSO, the solvent control), 156, 313, and 625 ug/ml in the absence of S-9 rat liver metabolic activation and at dose levels of 0, 100, 120, and 140 ug/ml in the presence of metabolic activation; both groups were treated for 6 hours followed by an 18-hour recovery period. In Experiment 2, the cell cultures were treated with the test article at dose levels of 0, 19.5, 39.1, and 78.1 ug/ml in the absence of metabolic activation for 24 hours and at dose levels of 0, 100, 120, and 140 ug/ml in the presence of metabolic activation for 6 hours followed by an 18-hour recovery period. Dividing cells were arrested at metaphase by treatment with colcemid 1.5 hours prior to the end of the incubation of the cells. The positive controls were functional. Dose-related chromosomal aberrations (primarily chromatid breaks and exchanges) were observed in test article treated cells in the presence of metabolic activation in both Experiments 1 and 2; no effect was observed on treated cells in the absence of metabolic activation. **Possible adverse effect: chromosomal aberrations in treated cells in the presence of metabolic activation. Acceptable.** (Corlett and Leung, 02/20/2015)

0025; 278997; "Micronucleus Test on S-1563 in Rats" (Kitamoto, S., Sumitomo Chemical Co., Ltd., Environmental Health Science Laboratory, Osaka, Japan, Study No. 4146, RWT-0007, 06/15/2010). 870.5395. S-1563 (Lot number 9CM0109G, purity = 95.7%) was suspended in corn oil and administered in a single dose to 5 to 10 Crl:CD(SD) rats per sex per dose at dose levels of 0 (vehicle only, 10 males, 10 females), 50 (5 females), 100 (5 females), 150 (5 males), 200 (10 females), 300 (5 males), and 600 (10 males) mg/kg). Also, 5 animals per sex were dosed with 60 mg/kg of the positive control compound cyclophosphamide. 5 animals per sex per dose

were sacrificed 24 hours after dosing and 5 animals per sex per dose at dose levels 0 (both sexes), 200 (females only), and 600 (males only) mg/kg were sacrificed 48 hours after dosing; all positive control animals were sacrificed after 24 hours. After sacrifice, the bone marrow cells from the femurs were examined: polychromatic erythrocytes were evaluated for the presence of micronuclei and the number of polychromatic erythrocytes in 1000 total erythrocytes (normochromatic plus polychromatic erythrocytes) was determined for each dose level. No treatment-related effects were observed. The positive control was functional. In conclusion, the results of this study indicate that under these test conditions, the test article does not induce micronuclei formation in the bone marrow cells of Crl:CD(SD) rats. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 02/25/2015)

DNA damage or miscellaneous effects

0025; 278998; "*In Vivo* Unscheduled DNA Synthesis (UDS) Assay with S-1563 in Rat Hepatocytes" (Tanaka, J., Biosafety Research Center, Foods, Drugs and Pesticides (BSRC), Shizuoka, Japan, Experiment No. C094(028-068), RWT-0013, 12/24/2010). 870.5550. S-1563 (Lot number 9CM0109G, purity = 95.7%) was suspended in corn oil and administered in a single dose to one group Crl:CD(SD) rats per dose at dose levels of 0 (vehicle only (corn oil), 4 males, 4 females), 100 (4 females), 200 (7 females), 300 (4 males), and 600 (6 males) mg/kg for 2 hours and to a second group consisting of the same number of animals and dose levels for 16 hours. Also, 4 animals per sex were dosed with positive control substances dimethylnitrosamine (DMN), (5 mg/kg, 2-hour group) and 2-acetylaminofluorene (2-AAF) (100 mg/kg, 16-hour group). 2 or 16 hours after the initiation of dosing, the livers from 4 animals per sex per dose were perfused *in situ*, the hepatocytes were isolated and cultured, and the hepatocytes from each of 3 animals were seeded separately into 2 chambers of one slide (resulting in 6 cell cultures per dose level). These cell cultures were cultured, washed, and medium containing [methyl-^{3}H] thymidine added. The cells were then cultured for 4 hours, washed, medium containing non-tritiated thymidine added, and the cells cultured overnight. The slides were processed and autoradiographs developed. 50 hepatocytes per chamber (100 per animal) were counted. The number of net nuclear grains was then calculated and the mean percent of cells in repair counted. The positive controls were functional. No treatment-related effects were observed; the results of this study indicate that under these test conditions, the test article does not induce unscheduled DNA synthesis in rat hepatocytes. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 03/03/2015)

REPRODUCTIVE TOXICITY, RAT

** 53304-0022; 278980; "S-1563: Two-Generation Reproduction Toxicity Study in the Han Wistar Rat"; (K. Pal-Kutas; Harlan Laboratories Ltd., 4414 Fullindorf, Switzerland; Study No. C84830; 8/10/12); Twenty four HanRcc:WIST rats/sex/group were treated in the diet with 0, 200, 500, or 1500 ppm of S-1563 (Momfluorothrin technical) (batch no. 9CM0109G; purity: 95.7%) for two generations. The treatment included 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation for the P1 generation. At that time, 24 F1 animals/sex/group were selected as parents and treated for 13 weeks prior to mating, followed by mating and 3 weeks each of gestation and lactation of the F2 generation. No treatment-related deaths occurred during the study. The mean body weights of both sexes in the 1500 ppm group of both generations were lower than those of the controls (NS, $p<0.01$ or 0.05). The mean food consumption of these animals was lower than that of the control animals as well (NS). The mean absolute and relative liver weights of both sexes in the 1500 ppm group for both generations and the mean relative liver weights of both sexes in the 500 ppm group of both generations were

greater than those of the control group (p<0.01 or 0.05). In the histopathological evaluation, centrilobular hypertrophy was noted in the livers of both sexes in the 1500 ppm group of both generations. There was no treatment-related effect upon the estrous cycling or sperm motility, morphology or sperm count in either generation. The mean time to sexual maturation was delayed for both sexes in the 1500 ppm F1 generation (p<0.05). Ovarian staging was not affected by the treatment for either generation. There were no treatment-related effects upon the fertility or gestation indices. The mean litter sizes were not affected by the treatment. There was no treatment-related effect upon pup viability. Mean pup weights for the 1500 ppm group of both generations were lower than those of the control group on days 14 and 21 of lactation (NS, p<0.05 or 0.01). The mean pup weights for the 500 ppm group in both generations were also less than those of the control group by day 21 post-natal (NS, p<0.01). **No adverse effect indicated. Parental NOEL:** 200 ppm (M: 14.1 mg/kg/day, F: 13.1 to 28.9 mg/kg/day) (based upon the increased relative liver weights of both sexes in the 500 ppm group); **Reproduction NOEL:** 1500 ppm (M: 113.3 mg/kg/day, F: 125 mg/kg/day) (based upon the lack of a treatment-related effect at the highest treatment level); **Developmental NOEL:** 200 ppm (F: 13.1 to 28.9 mg/kg/day) (based upon lower mean pup weights during lactation of the 500 ppm group of both generations); **Study acceptable.** (Moore, 3/17/15)

DEVELOPMENTAL TOXICITY

Rat

53304-0023; 278981; "Study on the Effect of Oral Administration of S-1563 on Embryo-Fetal Development in Rats" (Izumi, H., Kumamoto Laboratory, Mitsubishi Chemical Medience Corporation, Kumamoto, Japan, Study No. P081121, RWT-0018, 03/23/2011). 870.3700. S-1563 (Lot No. 9CM0109G, purity = 95.7%), suspended in corn oil, was administered orally by gavage once daily to 24 Crl:CD (SD) mated female rats at doses levels of 0 (corn oil only), 10, 25, or 75 mg/kg/day from gestation day 6 to gestation day 19. No maternal mortalities occurred. Tremors were observed sporadically in 6 dams at 75 mg/kg/day after dosing between days 15 and 19 of gestation. No treatment-related effect on corrected (gravid uterus removed) mean dam weight gain. There were no treatment-related effects on any of the developmental parameters of the fetuses. **No adverse effects. Maternal NOEL:** 25 mg/kg/day (based on the observation of tremors); **Developmental NOEL:** 75 mg/kg/day (based on no effects at the highest dose tested). **Acceptable.** (Corlett and Leung, 03/11/2015)

Rabbit

0023; 278982; "Study for Effects on Embryo-Fetal Development of S-1563 Administered Orally to Rabbits" (Iwashita, K., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. 4170, RWT-0020, 03/23/2011). 870.3700. S-1563 (Lot No. 9CM0109G, purity = 95.7%), suspended in a 0.5 % aqueous solution of methylcellulose, was administered orally by gavage once daily to 24 artificially inseminated female Kbl:NZW rabbits at doses levels of 0 (vehicle only), 100, 300, or 1000 mg/kg/day from gestation day 6 to gestation day 27. No maternal mortalities occurred. A treatment-related decrease in mean food consumption and the suppression of mean body weight gain was observed in the maternal animals on gestation day 9 at 300 and 1000 mg/kg/day. Necropsy on the maternal animals revealed no treatment-related macroscopic abnormalities. There were no treatment-related effects on any of the developmental parameters of the fetuses. **No adverse effects. Maternal NOEL:** 100 mg/kg/day (based on a decrease in mean food consumption and suppression of

mean body weight gain on gestation day 9); **Developmental NOEL:** 1000 mg/kg/day (based on no effects at the highest dose tested).

NEUROTOXICITY

Rat Acute Neurotoxicity Study

0027; 279000; "S-1563: Acute Oral Neurotoxicity Study in Rats" (Shutoh, Y., The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 11-0062, RWT-0069, 09/19/2012). 870.6200. S-1563 (Technical grade) (Lot No. 9CM0109G, purity = 95.7%), suspended in corn oil, was administered by gavage in a single dose to 10 Sprague-Dawley (Crl:CD(SD)) rats per sex per dose at dose levels of 0 (vehicle control), 30, 80, or 200 mg/kg. One female at 200 mg/kg died the day after test article administration; no other animals died prior to the scheduled sacrifice. Daily general clinical observations revealed wetted fur in the perianal region in 2 females at 200 mg/kg 1 day after treatment with this sign clearing in both animals 2 days after treatment and soiled fur in the perianal region was observed in 1 male at 200 mg/kg 2 days after treatment with this sign clearing 3 days after treatment. No other clinical signs were observed during the 14-day observation period. Detailed clinical observations conducted approximately 6 hours after test article administration (determined to be the time of peak effect) revealed treatment-related straub tail (in both sexes), salivation (in males), and tremors (in females) at 200 mg/kg; no treatment-related effects were observed on days 7 and 14. Motor activity assessments revealed no treatment-related effects on days 0, 7, and 14. No treatment-related effects on body weight were observed. Macroscopic examination revealed no treatment-related abnormalities. Microscopic examination of preserved nervous system tissues revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M/F) = 80 mg/kg (based on detailed clinical observations at the time of peak effect: salivation in males, tremors in females, straub tail in both sexes). A**cceptable.** (Corlett and Leung, 01/26/2015)

Rat Neurotoxicity Range-Finding and Peak Effect Time Study

0026; 278999; "S-1563: Dose Range-Finding Study for Acute Neurotoxicity Study in Rats" (Shutoh, Y., The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 11-0061, RWT-0042, 01/26/2012). Technical grade S-1563 (Lot No. 9CM0109G, purity = 97.5%), suspended in corn oil, was administered by gavage in a single dose to 3 Sprague-Dawley (Crl:CD(SD)) rats per sex per dose at dose levels of 0 (vehicle control), 60, 200, or 400 mg/kg. All animals were observed for morbidity and mortality twice a day. Detailed clinical observations were carried out in and outside the home cage (in an open field) on all animals after administration every hour for 8 hours and once a day thereafter. The animals were sacrificed 2 days after administration. All animals survived until the scheduled sacrifice. Daily observations revealed miosis in females at all dose levels that cleared in all animals 2 days after test article administration. Detailed clinical observations revealed treatment-related tremors (in both sexes at 200 and 400 mg/kg), twitching (in males at 400 mg/kg and in females at all dose levels), straub tail (in males at 200 and 400 mg/kg and in females at all dose levels), abnormal (asthenic) gait (in both sexes at 400 mg/kg), salivation (in males at 200 and 400 mg/kg), hunched posture (in males at 400 mg/kg), a decrease in muscle tone (in males at 400 mg/kg), and increased reactivity to handling (in both sexes at 400 mg/kg). Necropsy revealed no treatment-related macroscopic findings. The time of peak effect on the day of test article administration was estimated to be 4 to 8 hours after administration. NOEL (M) = 60 mg/kg/day and NOEL (F) < 60 mg/kg based on observed clinical signs. **Supplemental study** (only 3 animals per sex per

dose group were used and the animals were observed for only 2 days after test article administration). (Corlett and Leung, 01/16/2015)

Rat Subchronic Neurotoxicity Study

0028; 279001; "S-1563: 13-Week Neurotoxicity Study in Rats" (Sommer, E.W., Harlan Laboratories Ltd., Itingen, Switzerland, Harlan Laboratories Study C99050, RWT-0039, 12/19/2011). 870.6200. S-1563 (Batch Number 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 12 RccHan:WIST (SPF) rats per sex per dose at dose levels of 0 (diet only), 600, 2000, or 6000 ppm (for males, 0, 36.75, 126.62, and 402.32 mg/kg/day, respectively, and for females, 0, 40.50, 134.93, and 425.14 mg/kg/day, respectively) for 91 days. All animals survived to the scheduled necropsy. No treatment-related clinical signs were observed during the daily clinical observations or during the weekly detailed physical observations. FOB assessments conducted during weeks 2, 5, 9, and 13 revealed no treatment-related effects. Motor activity assessments conducted during weeks 2, 5, 9, and 13 revealed no treatment-related effects on horizontal activity (total distance) and vertical activity (rearing). A treatment-related decrease in mean body weight was observed in both sexes at 2000 and 6000 ppm. No treatment-related effect on mean relative brain weight was observed. Necropsies on the test animals revealed no macroscopic findings. Neuropathological examination of the central and peripheral nervous system tissues revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M) = 36.75 mg/kg/day (600 ppm) and NOEL (F) = 40.50 mg/kg/day (600 ppm) based on a decrease in mean body weight. **Acceptable.** (Corlett and Leung, 02/04/2015)

Developmental neurotoxicity, rat

Not required at this time per USEPA Memorandum of January 20, 2010, Pyrethroids: Evaluation of Data from Developmental Neurotoxicity Studies and Consideration of Comparative Sensitivities.

Delayed neurotoxicity, hen

Not performed nor required.

IMMUNOTOXICITY

Rat 4-Week Immunotoxicity Study

0032; 279006; "S-1563- A 28-Day Oral (Dietary) Immunotoxicity Study in Male Wistar Han Rats" (Hosako, H., WIL Research, Ashland, OH and ImmunoTox, Inc., Richmond, VA, Laboratory Project ID: WIL-118068, RWT-0068, 09/21/2012). 870.7800. S-1563 (Lot no. 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 10 male Wistar Han HanRcc:WIST (SPF) rats per dose at dose levels of 0 (diet only), 300, 1000, or 3000 ppm (average test article consumption 0, 26, 81, and 241 mg/kg/day, respectively) for 28 consecutive days. On study day 24 of test article administration, all animals in the study were immunized with an intravenous injection (via the tail vein) of 2 x 10^8 sheep red blood cells (sRBC). Spleens collected from these immunized animals at the scheduled necropsy were used for the splenic antibody-forming cell (AFC) assay to assess the T-cell dependent antibody response (TDAR). All animals survived to the scheduled necropsy. No test article-related clinical signs were observed during the daily clinical observations or during the weekly detailed physical examinations. Treatment-related decreases in mean body weight gain and mean food consumption were observed at 3000 ppm. No treatment-related effect on mean relative thymus and spleen weights were observed. Macroscopic examination revealed no treatment-related

abnormalities. No treatment-related effects on mean spleen cell numbers, on mean antibody-forming cells (AFC)/10^6 spleen cells, or on mean AFC/spleen were observed. The positive control (cyclophosphamide monohydrate) was functional. **No adverse effects**. NOEL (M) = 81 mg/kg/day (1000 ppm) based on a decrease in mean body weight gain and a decrease in mean food consumption. **Acceptable.** (Corlett and Leung, 03/23/2015)

ENDOCRINE DISRUPTOR STUDIES

Not required at this time.

SUPPLEMENTAL STUDIES

Mode of Action Studies

0023; 278983; "Study for Mode of Action Analysis for Tumor Formation of S-1563 on Rat Liver (1) - Time Course Analysis in Male Rats-" (Okuda, Y., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. S1498, RWT-0079, 12/03/2012). S-1563 (Lot No. 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 2 groups of 10 male HarlanRccHanTM:WIST rats (10 weeks old) per dose at dose levels of 0 (basal diet only) and 3000 ppm with one group treated for 7 days and the other group treated for 14 days. Average chemical intake for the 7-day treatment group was 147 mg/kg/day and for the 14-day treatment group it was 175 mg/kg/day. All animals were observed for mortality once a day and body weights were measured on days 1 (prior to dosing), 3, 6, and 8 for the 7-day treatment group and on days 1, 3, 7, 10, 14, and 15 for the 14-day treatment group. Liver weight, gross pathology, liver histopathology, hepatocellular proliferation rate (determined as 5-bromo-2'-deoxyuridine (BrdU) labeling indices), and hepatic CYP mRNA expression levels were examined. All animals survived until the scheduled sacrifice. Treatment-related increased mean relative liver weight and increased expression of CYP2B1/2 mRNA were observed after both 7- and 14-day treatment periods. Necropsy revealed no treatment-related macroscopic findings. No statistically significant increase in hepatocellular proliferation rate was observed in this study. **Supplemental study** (not a guideline study). (Corlett and Leung, 04/03/2015)

0023; 278984; "Study for Mode of Action Analysis for Tumor Formation of S-1563 on Rat Liver (2) - Analysis of Time Course, Dose Response, and Reversibility in Male Rats-" (Okuda, Y., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. S1528, RWT-0080, 12/05/2012). S-1563 (Lot No. 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 3 groups of 10 10-week old male HarlanRccHanTM:WIST rats per dose. Group 1 (main group) consisted of dose levels of 0 (basal diet only), 200, 500, 1500, 3000, and 6000 ppm and were treated for 7 days, group 2 (recovery group) consisted of dose levels of 0 and 3000 ppm and were treated for 7 days followed by a 7-day recovery period, and group 3 (satellite group) consisted of dose levels 0, 3000, and 6000 ppm and were treated for 14 days (average chemical intake values for the main group were 11.6, 28.7, 80.6, 163.3, and 257.7 mg/kg/day, respectively, for the recovery group 167.8 mg/kg/day, and for the satellite group 166.1 and 340.2 mg/kg/day, respectively). All animals were observed for mortality once a day and body weights were measured on days 1 (prior to dosing), 3, and 8 for the main group and on days 1, 3, 8, and 15 for the recovery and satellite groups. Body weight, liver weight, gross pathology, liver histopathology (light and electron microscopy), and hepatic enzyme activities (CYP2B and CYP4A) were examined. All animals survived until the scheduled sacrifice. A decrease in mean body weight was observed at dose levels of 1500 ppm and above in the main group possibly due to palatability issues; recovery group body weight data indicate that body

weight suppression was reversible. Treatment-related increased mean relative liver weight was observed in both the 7-day and the 14-day treatment groups at 3000 and 6000 ppm; this effect was not observed in the recovery group animals. Necropsy revealed treatment-related enlarged liver at 3000 and 6000 ppm in the 14-day treatment group but not in the 7-day treatment group; this effect was observed in 1/10 animals at 3000 ppm in the recovery group animals. Histopathology (using light microscopy) revealed treatment-related hepatocellular hypertrophy at 3000 and 6000 ppm in both the 7-day and 14-day treatment groups; this effect was not observed in the recovery group animals. A treatment-related increase in mean CYP2B activity was observed at 3000 and 6000 ppm in the 7-day treatment group; this effect was not observed in the recovery group animals. NOEL (M) = 80.6 mg/kg/day (1500 ppm) based on 7-day treatment group relative liver weight, histopathology, and CYP2B activity data. **Supplemental study** (not a guideline study). (Corlett and Leung, 04/07/2015)

0024; 278985; "Study for Mode of Action Analysis for Tumor Formation of S-1563 on Rat Liver (3) - Time Course Analysis at High Dose of S-1563 in Male Rats -" (Okuda, Y., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. S1573, RWT-0081, 12/05/2012). S-1563 (Lot No. 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 2 groups of 10 10-week old male HarlanRccHanTM:WIST rats per dose at dose levels of 0 (basal diet only), 3000, and 6000 ppm. In one group (main group), the animals were treated for 7 days and in the other group (satellite group), the animals were treated for 14 days (average chemical intake values for the main group were 148.6, and 299.0 mg/kg/day, and for the satellite group 159.6 and 321.5 mg/kg/day, respectively). All animals were observed for mortality once a day and body weights were measured on days 1 (prior to dosing), 3, and 8 for the main group and on days 1, 3, 8, and 15 for the satellite group. Body weight, liver and thyroid weights, gross pathology, liver and thyroid histopathology (light microscopy), hepatocellular proliferation rate (determined as 5-bromo-2'-deoxyuridine (BrdU) labeling indices), hepatic UGP-glucuronosyltransferase activity, and serum triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) levels were determined. All animals survived until the scheduled sacrifice. A decrease in mean body weight was observed at dose levels of 3000 and 6000 ppm in both the 7-day and 14-day exposure groups on exposure day 3 and at dose levels 3000 and 6000 ppm in the 7-day exposure group and at dose level 6000 ppm in the 14-day exposure group on exposure day 8 possibly due to palatability issues; this decreased body weight effect was not observed on exposure day 15 in the 14-day exposure group indicating that body weight suppression was reversible. Treatment-related increased mean relative liver weight was observed in both the 7-day and the 14-day treatment groups at 3000 and 6000 ppm; no effect on mean relative thyroid weights was observed in either the 7-day or 14-day treatment group animals. Necropsy revealed enlarged liver in the 7-day treatment group animals at 6000 ppm and in 14-day treatment group animals at 3000 and 6000 ppm. Histopathology (using light microscopy) revealed treatment-related hepatocellular hypertrophy at 3000 and 6000 ppm in both the 7-day and 14-day treatment groups and treatment-related follicular hypertrophy in the thyroid at 6000 ppm in the 14-day treatment group. A treatment-related increase in replicative DNA synthesis (determined by BrdU labeling indices) was observed at 3000 and 6000 ppm in both the 7-day and 14-day treatment groups but less so in the 14-day group. A statistically significant but slight increase in hepatic UGT activity was observed at 3000 and 6000 ppm in both the 7-day and 14-day treatment groups. Examination of the T3, T4, and TSH serum levels revealed no treatment-related effects. **Supplemental study** (not a guideline study). (Corlett and Leung, 04/09/2015)

0024; 278986; "Study for Mode of Action Analysis for Tumor Formation of S-1563 on Rat Liver (4) - The 2nd Study for Dose Response Analysis in Male Rats-" (Okuda, Y., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. S1585, RWT-0082, 12/05/2012). S-1563 (Lot No. 9CM0109G, purity = 95.7%) was admixed to the diet and fed to 10 10-week old male HarlanRccHanTM:WIST rats per dose at dose levels of 0 (basal diet only), 200, 500, 1500, and 3000 ppm for 7 days (average chemical intake values were 11.6, 28.5, 75.9, 137.4 mg/kg/day, respectively). Also, a group of 10 male rats were fed basal diet containing 1000 ppm of phenobarbital (PB, average chemical intake value was 57.6 mg/kg/day), a positive control as a constitutive androstane receptor (CAR) activator. All animals were observed for mortality once a day and body weights were measured on days 1 (prior to dosing), 3, and 8. Liver and thyroid weights, gross pathology, liver and thyroid histopathology (light microscopy), hepatocellular proliferation rate (determined as 5-bromo-2'-deoxyuridine (BrdU) labeling indices), and hepatic cytochrome P450 CYP2B activity (in 6 animals) were determined. All animals survived until the scheduled sacrifice. A decrease in mean body weight was observed at 3000 ppm on exposure day 3 but not on exposure day 8 indicating that body weight suppression was reversible. Treatment-related increased mean relative liver weight was observed at 1500 and 3000 ppm; no effect on mean relative thyroid weights was observed. Necropsy revealed enlarged liver in 4 of 10 animals at 3000 ppm; no other treatment-related abnormalities were observed. Histopathology (using light microscopy) revealed slight centrilobular hepatocellular hypertrophy in 2 of 10 animals at 3000 ppm; no other treatment-related abnormalities were observed. A treatment-related increase in replicative DNA synthesis (determined by BrdU labeling indices) was observed at 1500 and 3000 ppm. A treatment-related increase in mean hepatic CYP2B activity was observed at 3000 ppm. The positive control was functional. NOEL (M) = 28.5 mg/kg/day (500 ppm) based on increased mean relative liver weight and an increase in replicative DNA synthesis. **Supplemental study** (not a guideline study). (Corlett and Leung, 04/14/2015)

0024; 278987; "Study for Mode of Action Analysis for Tumor Formation of S-1563 on Rat Liver (5) - Analysis for Time Course and Dose Response in Female Rats -" (Okuda, Y., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study No. S1595, RWT-0083, 12/05/2012). S-1563 (Lot No. 9CM0109G, purity = 95.7%) was admixed to the diet and fed to one group (main group) of 10 10-week old female HarlanRccHanTM:WIST rats per dose at dose levels of 0 (basal diet only), 200, 500, 1500, and 3000 ppm for 7 days (average chemical intake values were 12.3, 31.2, 79.7, and 150.9 mg/kg/day, respectively) and to another group (satellite group) of 10 10-week old female rats per dose at dose levels of 0 and 3000 ppm for 14 days (average chemical intake of 163.8 mg/kg/day). All animals were observed for mortality once a day and body weights were measured on days 1 (prior to dosing), 3, and 8 for the main group and on days 1, 3, 8, and 15 for the satellite group. Liver weights, gross pathology, liver histopathology (light microscopy), hepatocellular proliferation rate (determined as 5-bromo-2'-deoxyuridine (BrdU) labeling indices), and hepatic cytochrome P450 CYP2B and CYP4A activities (in 6 animals per dose in both groups) were determined. All animals survived until the scheduled sacrifice. A statistically significant decrease in mean body weight was observed at days 3, 8, and 15 in the treated animals in the satellite group but not at any dose level in the animals in the main group. A treatment-related increase in mean relative liver weight was observed at 1500 and 3000 ppm in the main group and

at 3000 ppm in the satellite group. Necropsy revealed no treatment-related abnormalities. Histopathology (using light microscopy) revealed slight, diffuse hepatocellular hypertrophy in 3 of 10 animals at 3000 ppm in the main group; no other treatment-related abnormalities were observed. A treatment-related increase in replicative DNA synthesis (determined by BrdU labeling indices) was observed at 1500 and 3000 ppm in the main group and at 3000 ppm in the satellite group (although somewhat attenuated when compared to the main group values). A treatment-related increase in mean hepatic CYP2B activity was observed at 1500 and 3000 ppm in the main group and at 3000 ppm in the satellite group; no effect on CYP4A activity was observed. NOEL (F) = 31.2 mg/kg/day (500 ppm) based on increased mean relative liver weight, an increase in replicative DNA synthesis, and an increase in mean CYP2B activity in the main group animals. **Supplemental study** (not a guideline study). (Corlett and Leung, 04/15/2015)

53304-0024; 278988; "Study for Mode of Action Analysis for Effects of S-1563 on Thyroid Gland in Male Rats"; (Y. Okuda; Environmental Health Sciences Laboratory, Sumitomo Chemical Company, Ltd., Konohanu-ku, Osaka, Japan; Study No. S1625; 12/5/12); Ten male Wistar rats/group received 0, 3000 or 10000 ppm of S-1563 (Momfluorothrin technical) (lot no. 9CM0109G; purity: 95.7%) in the diet for either 7 (146.0, 406.5 mg/kg/day) or 14 days (157.2, 497.2 mg/kg/day). No deaths occurred during the treatment period. The mean body weight gains of both treatment groups were less than those of the control groups over the 1st week of treatment ($p<0.01$ or 0.05). Food consumption was less for these groups over this period of treatment as well. The mean absolute and relative liver weights of both the 3000 and 10000 ppm groups in both treatment scenarios were greater than the control values ($p<0.01$). In the histopathological examination, diffuse hepatocellular hypertrophy was noted in the livers of both the 3000 and 10000 ppm groups of both treatment scenarios. An increased incidence of follicular cell hypertrophy was also evident in the 3000 and 10000 ppm groups of both treatment cohorts. In the serum hormone analysis, the T4 levels were lower than the control value for both the 3000 and 10000 ppm groups in the 7-day treatment group. After 14 days of treatment, this effect was less apparent. **No adverse effect indicated. Rat 14-day Dietary Toxicity NOEL:** (M) < 3000 ppm (146.7 mg/kg/day) (based upon the histological effects noted in the livers and thyroid glands of the 3000 ppm treatment group). **Study supplemental.** (Moore, 4/14/15)

53304-0024; 278989; "Study for Mode of Action Analysis for Tumor Formation of S-1563 in Rat Liver (6): - *In Vitro* Evaluation for Role of Nuclear Receptor CAR in S-1563- and Its Metabolite Z-CMCA-induced CYP2B1/2 mRNA Expression of Cultured Rat Hepatocytes"; (Y. Okuda; **:** Environmental Health Sciences Laboratory, Sumitomo Chemical Company, Ltd., Konohanu-ku, Osaka, Japan; Study No. S1473; 12/11/12); A primary culture of rat hepatocytes were transfected with siRNA (short-interfering RNA) for CAR (constitutive androstane receptor) or Negative Control (Stealth RNAi (RNA-interference) Negative Control). Following 4 hours of treatment, the cells were exposed to 50 or 500 µM of phenobarbital (PB) or 100 µM of S-1563 or 1000 µM of Z-CMCA (metabolite of S-1563) for 2 days (these treatment levels had previously been shown to induce CYP2B-dependent enzyme activity in rat hepatocytes). On day 3, total RNA was extracted from the cells. Complementary DNA was prepared from the total RNA by reverse transcription. PCR assays for rat CYP2B1/2 and CAR were performed through 40 cycles. Levels of mRNA for these two entities as well as for glyceraldehyde 3-phosphate dehydrogenase mRNA (as an internal control) were ascertained. Exposure of the hepatocytes to S-1563 and Z-CMCA was shown to increase the mRNA expression for CYP2B1/2. However,

by means of the RNA interference technique, when the induction of CAR mRNA was interfered with, this increase in the expression of CYP2B1/2 was greatly diminished both for the positive control, phenobarbital and for S-1563 and Z-CMCA. Based on these results, the mode of action for S-1563 and Z-CMCA was surmised to be mediated through the constitutive androstane receptor. **Study supplemental.** (Moore, 4/7/15)

53304-0024; 278990; "Study for Mode of Action Analysis for Effects of S-1563 on Male Mouse Liver-Dose Response and Reversibility"; (T. Yamada; Environmental Health Sciences Laboratory, Sumitomo Chemical Company, Ltd., Konohanu-ku, Osaka, Japan; Study No. S1533; 11/28/12); Ten male CD1 mice/group received 0, 600, 2500 or 5500 ppm of S-1563 (lot no. 9CM0109G; purity: 95.7%) in the diet for 7 days (73.3, 286.0, 636.4 mg/kg/day). A recovery cohort of 10 males/group was included in the control and 5500 ppm groups and maintained for an additional 7 days after completion of the treatment (680.5 mg/kg/day). 5-bromo-2'-deoxyuridine (BrdU)-containing osmotic pumps were implanted subcutaneously 8 days prior to the scheduled euthanasia. Upon euthanasia, hepatic 7-pentoxyresorufin O-depentylase (PROD) was assayed as a measure of CYP2B activity. Lauric acid hydroxylation was used as a measure of CYP4A activity. The 5500 ppm treatment group in the main study group demonstrated reduced body weight gain and food consumption during the first 3 days of treatment ($p<0.01$ or 0.05). The mean absolute and relative liver weights of the 2500 and 5500 ppm groups in the main study were greater than the control values ($p<0.01$ or 0.05). No effect on the liver weights was apparent by 7 days post-final treatment. Histopathological examination of the livers revealed treatment-related hepatocellular centrilobular hypertrophy in animals in the 2500 and 5500 ppm groups ($p<0.01$ or 0.05). Electron microscopic examination of the livers from the 5500 ppm animals revealed proliferation of the smooth endoplasmic reticulum and increased lipid droplet formation. The rate of hepatocellular proliferation (BrdU incorporation) was significantly increased in the livers of the 5500 ppm animals. PROD activity was enhanced for the 600 ppm group and above in a treatment-related manner ($p<0.05$). Lauric acid hydroxylation was significantly increased in the livers of the 5500 ppm animals ($p<0.01$). All observed effects in the liver were no longer apparent after 7 days of recovery. **No adverse effect indicated. Mouse 7-Day Dietary Toxicity NOEL:** 600 ppm (based upon the increased absolute and relative livers weights and histopathological lesions in the livers of the 2500 ppm group); **Supplemental study** (Moore, 4/8/15)

53304-0024; 278991; "Study for Mode of Action Analysis for Effects of S-1563 on Male Mouse Liver-Time Course Analysis"; (T. Yamada; Environmental Health Sciences Laboratory, Sumitomo Chemical Company, Ltd., Konohanu-ku, Osaka, Japan; Study No. S1497; 11/28/12); Ten male CD-1 mice/group were treated in the diet with 0 or 5500 ppm of S-1563 (lot no. 9CM0109G; purity: 95.7%) for either 7 (740 mg/kg/day) or 14 (760.3 mg/kg/day) days. 5-bromo-2'-deoxyuridine (BrdU)-containing osmotic pumps were implanted subcutaneously 8 days prior to the scheduled euthanasia. Total RNA was extracted from the liver and hepatic cytochrome enzymes, CYP2B10 and CYP4A10 mRNA expression analysis was performed by means of the PCR (polymerase chain reaction) assay. The 5500 ppm treatment group for both treatment periods demonstrated reduced body weight gain and food consumption during the first 3 days of treatment ($p<0.01$ or 0.05). The mean absolute and relative liver weights of the two 5500 ppm groups were greater than the control values ($p<0.01$). Histopathological examination of the livers revealed treatment-related hepatocellular centrilobular hypertrophy in animals of

both 5500 ppm groups (NS or p<0.01). The rate of hepatocellular proliferation (BrdU incorporation) was increased in the livers of the 5500 ppm animals for both treatment periods (p<0.01 or 0.05). **Study supplemental.** (Moore, 4/8/15)

53304-0025; 278992; "Study for Mode of Action Analysis for Effects of S-1563 on Female Mouse Liver-Time Course, Dose Response and Reversibility"; (T. Yamada; **:** Environmental Health Sciences Laboratory, Sumitomo Chemical Company, Ltd., Konohanu-ku, Osaka, Japan; Study No. S1556; 11/28/12); In the first cohort, 10 female CD1 mice/group received 0, 600, 2500 or 5500 ppm of S-1563 (Momfluorothrin technical) (lot no. 9CM0109G; purity: 95.7%) in the diet for 7 days (69.0, 292.3, 492.3 mg/kg/day). In the second cohort, 10 females/group received 0 or 5500 ppm of the test material for 14 days (673.7 mg/kg/day). In the 3rd cohort, 6 females/group received 0 or 5500 ppm of the test material for 7 days, followed by maintenance on control diet for an additional 7 days (548.7 mg/kg/day). 5-bromo-2'-deoxyuridine (BrdU)-containing osmotic pumps were implanted subcutaneously 8 days prior to the scheduled euthanasia. Upon euthanasia, hepatic 7-pentoxyresorufin O-depentylase (PROD) was assayed as a measure of CYP2B activity. Lauric acid hydroxylation was used as a measure of CYP4A activity. In the 1st cohort, the total number of animals in the 5500 ppm group was reduced to 8, one animal died and one was removed from the study for an unexplained reason. The 5500 ppm treatment groups in all three cohorts demonstrated reduced body weight gain and food consumption during the first 3 days of treatment (p<0.01 or 0.05). Thereafter no treatment-related effect was evident. The mean absolute and relative liver weights of the 5500 ppm groups in the 7- and 14-day treatment cohorts and the 2500 ppm group in the 7-day treatment cohort were greater than the control values (p<0.01). No effect on the liver weight was evident for the 7-day treatment with a 7-day recovery cohort. Similar results in the histpathological examination were noted. Centrilobular hepatocellular hypertrophy was evident in the livers of those animals in the same groups demonstrating increased absolute and relative weight increases. However, the effect was not present for the animals with the 7-day recovery period. Electron microscopic examination of liver tissue from animals in the control and 5500 ppm groups of the 7-day treatment cohort revealed a slight increase in the proliferation of the smooth endoplasmic reticulum in the livers of the treatment group. BrdU labeling was increased in the livers of the 2500 and 5500 ppm groups which received 7-days of treatment (p<0.01 or 0.05). Although the labeling was increased for the animals in the 5500 ppm after 14-days of treatment, the increase was not statistically significant. The S9 fraction concentration and CYP2B and CYP4A activity levels were increased for the 600 ppm treatment group and above in a treatment-related manner in the 7-day treatment cohort and for the 5500 ppm group in the 14-day treatment cohort (p<0.01 or 0.05). This effect was not noted for the 5500 group in the 7-day treatment with the 7-day recovery. **No adverse effect indicated. Mouse 7-Day Dietary Toxicity NOEL:** 600 ppm (based upon the increased absolute and relative livers weights and histopathological lesions in the livers of the 2500 ppm group); **Supplemental study** (Moore, 4/14/15)